WHAT IS CLAIMED IS:

1. A mutant α subunit comprising an amino acid substitution at position 22 of the amino acid sequence of the α subunit as depicted in Figure 1 (SEQ ID NO:1).

2. The mutant α subunit of claim 1 wherein the amino acid substitution at position 22 is arginine.

3. The mutant α subunit of claim 1 which is purified.

4. The mutant α subunit of claim 1 further comprising one or more amino acid substitutions in amino acid residues selected from among positions 11-21 of the amino acid sequence of the α subunit as depicted in Figure 1 (SEQ ID NO:1).

5. The mutant α subunit of claim 4 wherein the one or more substitutions are amino acids selected from the group consisting of arginine and lysine.

6. The mutant α subunit of claim 4 wherein the one or more amino acid substitutions are in amino acid residues selected from among positions 11, 13, 14, 16, 17, and 20 of the amino acid sequence of the α subunit as depicted in Figure 1 (SEQ ID NO:1).

7. The mutant α subunit of claim 1 further comprising one or more amino acid substitutions in the β hairpin L1 loop of the α subunit.

8. The mutant α subunit of claim 7 wherein the one or more substitutions are amino acids selected from the group consisting of arginine and lysine.

9. The human α subunit of claim 4 wherein the one or more substitutions are selected from the group consisting of αT11K, αQ13K, αE14K, αP16K, αF17R, and αQ20K.

10. A mutant α subunit in which the only mutation is an amino acid substitution at position 22 of the amino acid sequence of the α subunit as depicted in Figure 1 (SEQ ID NO:1).

11. The mutant α subunit of claim 10 wherein the substitution at position 22 is arginine.

12. The mutant α subunit of claim 10 which is purified.

13. A mutant TSH heterodimer comprising a mutant α subunit comprising an amino acid substitution at position 22 of the amino acid sequence of the α subunit as depicted in Figure 1 (SEQ ID NO:1) and a β subunit, wherein the bioactivity of the

mutant TSH heterodimer is greater than the bioactivity of the wild type TSH heterodimer.

14. The mutant TSH heterodimer of claim 13 wherein the amino acid substitution at position 22 is arginine.

15. The mutant TSH heterodimer of claim 13 which is purified.

16. The mutant TSH heterodimer of claim 13 in which the β subunit is a human β subunit.

17. The mutant TSH heterodimer of claim 17 wherein the one or more substitutions are amino acids selected from the group consisting of arginine and lysine.

18. The mutant TSH heterodimer of claim 13 further comprising one or more amino acid substitutions in amino acid residues selected from among positions 11-21 of the amino acid sequence of the α subunit as depicted in Figure 1 (SEQ ID NO: 1).

19. The mutant TSH heterodimer of claim 13 wherein the one or more amino acid substitutions are in amino acid residues selected from among positions 11, 13, 14, 16, 17, and 20 of the amino acid sequence of the α subunit.

20. The mutant TSH heterodimer of claim 13 further comprising one or more amino acid substitutions in the β hairpin L1 loop of the α subunit.

21. The mutant TSH heterodimer of claim 20 wherein the one or more substitutions are amino acids selected from the group consisting of arginine and lysine.

22. The mutant TSH heterodimer of claim 17 wherein the one or more substitutions are selected from the group consisting of αT11K, αQ13K, αE14K, αP16K, αF17R, and αQ20K.

23. A mutant TSH heterodimer in which the only mutation is an amino acid substitution at position 22 of the amino acid sequence of the α subunit as depicted in Figure 1 (SEQ ID NO:1).

24. The mutant TSH heterodimer of claim 23 wherein the substitution at position 22 is arginine.

25. The mutant heterodimer of claim 23 which is purified.

26. A mutant TSH heterodimer comprising (a) a TSH β subunit joined via a peptide bond at its carboxyl terminus to the amino terminus of the carboxyl terminal extension peptide of human chorionic gonadotropin and (b) an α subunit, wherein at

least the TSH β subunit or the TSH α subunit contains at least one amino acid substitution, and wherein the bioactivity of the mutant TSH heterodimer is greater than the bioactivity of wild type TSH heterodimer.

27. The mutant TSH heterodimer of claim 26 wherein the at least one amino acid substitution is in amino acid residues selected from among positions 11-21 of the amino acid sequence of human α subunit as depicted in Figure 1 (SEQ ID NO:1).

28. The mutant human TSH heterodimer of claim 26 wherein the at least one amino acid substitution is in amino acid residues selected from among positions 58-69 of the amino acid sequence of TSH β subunit as depicted in Figure 2 (SEQ ID NO: 2).

29. The mutant human TSH heterodimer of claim 28 wherein the at least one amino acid substitution is selected from the group consisting of βI58R, βE63R and βL69R.

30. The mutant TSH heterodimer of claim 26 comprising a mutant human α subunit and a mutant human TSH β mutant subunit, wherein the mutant human α subunit comprises at least one amino acid substitution in amino acid residues selected from among positions 11-22 of the amino acid sequence of human α subunit as depicted in Figure 1 (SEQ ID NO: 1), and wherein the mutant human TSH β subunit comprises at least one amino acid substitution in amino acid residues selected from among positions 58-69 of the amino acid sequence of human TSH β subunit as depicted in Figure 2 (SEQ ID NO: 2).

31. The mutant TSH heterodimer of claim 26 which is a mutant of a human TSH heterodimer.

32. A TSH analog comprising an α subunit which is covalently bound to a TSH β subunit, wherein at least one of the subunits comprises at least one amino acid substitution in its amino acid sequence, and wherein the bioactivity of said TSH analog is greater than the bioactivity of a TSH analog comprising a wild-type α subunit covalently bound to a wild-type TSH β subunit.

33. The TSH analog of claim 32 wherein the at least one amino acid substitution is in amino acid residues selected from among positions 11-22 of the amino acid sequence of α subunit as depicted in Figure 1 (SEQ ID NO: 1).

34. The TSH analog of claim 32 wherein the at least one amino acid substitution is in amino acid residues selected from among positions 58-69 of the amino acid sequence of human TSH β subunit as depicted in Figure 2 (SEQ ID NO: 2).

35. The TSH analog of claim 32 in which both the αsubunit and the β TSH subunit comprise one or more amino acid substitutions.

36. The TSH analog of claim 35 in which the α subunit has at least one amino acid substitution in amino acid residues selected from among positions 11-22 of the amino acid sequence of human α subunit as depicted in Figure 1 (SEQ ID NO: 1), and the TSH β subunit has at least one amino acid substitution selected from among positions 58-69 of the amino acid sequence of human TSH β subunit as depicted in Figure 2 (SEQ ID NO: 2).

37. The TSH analog of claim 32 in which the TSH β subunit is joined via a peptide bond at the carboxyl terminus to the amino terminus of the carboxyl terminal extension peptide of human chorionic gonadotropin, and in which the carboxyl terminus of the carboxyl terminal extension peptide is joined via a peptide bond to the amino terminus of α subunit.

38. The TSH analog of claim 32 in which the TSH β subunit is joined via a peptide bond at the carboxyl terminus to the amino terminus of the α subunit.

39. The mutant TSH heterodimer of claim 26 wherein the hormonal half life in circulation in vivo of the mutant TSH heterodimer is greater than the wild type TSH.

40. The mutant TSH analog of claim 32 wherein the hormonal half life in circulation in vivo of the mutant TSH analog is greater than the wild type TSH.

41. A nucleic acid comprising a nucleotide sequence encoding the mutant α subunit of claim 1.

42. A nucleic acid comprising a nucleotide sequence encoding the TSH analog of claim 32, in which the α subunit is joined to the β-subunit via a peptide bond.

43. A method of treating or preventing hypothyroidism comprising administering to a subject in which such treatment or prevention is desired an amount of the TSH heterodimer of claim 26 sufficient to treat or prevent hypothyroidism.

44. A method of treating or preventing hypothyroidism comprising administering to a subject in which such treatment or prevention is desired an amount of the TSH analog of claim 32 sufficient to treat or prevent hypothyroidism.

45. A method of treating thyroid cancer comprising administering to a subject in which such treatment or prevention is desired an amount of the mutant TSH heterodimer of claim 26 sufficient to stimulate iodine uptake and subsequently administering to said subject an amount of radiolabelled iodine sufficient to treat thyroid cancer.

46. A method of treating thyroid cancer comprising administering to a subject in which such treatment or prevention is desired an amount of the TSH analog of claim 30 sufficient to stimulate iodine uptake and subsequently administering to said subject an amount of radiolabelled iodine sufficient to treat thyroid cancer.

47. A method of diagnosing thyroid cancer comprising administering to a subject an amount of the mutant TSH heterodimer of claim 26 sufficient to stimulate uptake of iodine by thyroid cancer cells and an amount of radiolabelled iodine sufficient to diagnose thyroid cancer; and detecting said radiolabelled iodine, wherein an increase relative to a subject not having thyroid disease in uptake of radiolabelled iodine indicates that the subject has thyroid cancer.

48. A method of diagnosing thyroid cancer comprising administering to a subject lacking non-cancerous thyroid cells an amount of the mutant TSH heterodimer of claim 24 sufficient to stimulate uptake of iodine by thyroid cancer cells and an amount of radiolabelled iodine sufficient to diagnose thyroid cancer; and detecting said radiolabelled iodine, wherein an increase in uptake of radiolabelled iodine indicates that the subject has thyroid cancer.

49. A method of diagnosing thyroid cancer comprising administering to a first subject an amount of the mutant TSH heterodimer of claim 26 sufficient to stimulate release of thyroglobulin in vivo and measuring the levels of thyroglobulin in said first subject, in which an increase in thyroglobulin levels relative to the thyroglobulin levels in a sample of a second subject not having thyroid cancer indicates that said first subject has thyroid cancer.

50. A method of diagnosing thyroid cancer comprising administering to a subject an amount of the TSH analog of claim 32 sufficient to stimulate uptake of iodine by thyroid cancer cells and an amount of radiolabelled iodine sufficient to diagnose thyroid cancer; and detecting said radiolabelled iodine, wherein an increase relative to a subject not having thyroid disease in uptake of radiolabelled iodine indicates that the subject has thyroid cancer.

51. A method of diagnosing thyroid cancer comprising administering to a subject lacking non-cancerous thyroid cells an amount of the mutant TSH heterodimer of claim 32 sufficient to stimulate uptake of iodine by thyroid cancer cells and an amount of radiolabelled iodine sufficient to diagnose thyroid cancer; and detecting said radiolabelled iodine, wherein an increase uptake of radiolabelled iodine indicates that the subject has thyroid cancer.

52. A method of diagnosing thyroid cancer comprising administering to a first subject an amount of the TSH analog of claim 32 sufficient to stimulate release of thyroglobulin in vivo and measuring the levels of thyroglobulin in said first subject, in which an increase in thyroglobulin levels relative to the thyroglobulin levels in a sample of a second subject not having thyroid cancer indicates that said first subject has thyroid cancer.

53. A method of diagnosing or screening for a disease or disorder characterized by the presence of antibodies against the TSH receptor comprising contacting cultured cells or isolated membrane containing TSH receptors with a sample putatively containing antibodies from a first subject and with a diagnostically effective amount of the radiolabelled mutant TSH heterodimer of claim 26; and measuring the binding of the radiolabelled mutant TSH to the cultured cells or isolated membrane, wherein a decrease in the binding of the radiolabelled TSH relative to the binding in the absence of said sample or in the presence of a sample of a second subject not having said disease or disorder, indicates the presence of said disease or disorder in said first subject

54. The method of claim 53 in which said disease or disorder is Graves' disease.

55. A method of diagnosing or screening for a disease or disorder characterized by the presence of antibodies against the TSH receptor comprising contacting cultured cells or isolated membrane containing TSH receptors with a sample putatively containing antibodies from a first subject and with a diagnostically effective amount of the radiolabelled TSH analog of claim 32; and measuring the binding of the radiolabelled mutant TSH to the cultured cells or isolated membrane, wherein a decrease in the binding of the radiolabelled TSH relative to the binding in the absence of said sample or in the presence of a sample of a second subject not having said disease or disorder, indicates the presence of said disease or disorder in said first subject.

56. The method of claim 55 in which said disease or disorder is Graves' disease.

57. A pharmaceutical composition comprising a therapeutically effective amount of the mutant TSH heterodimer of claim 13; and a pharmaceutically acceptable carrier.

58. A pharmaceutical composition comprising a therapeutically effective amount of the mutant TSH heterodimer of claim 26; and a pharmaceutically acceptable carrier.

59. A pharmaceutical composition comprising a therapeutically effective amount of the TSH analog of claim 32; and a pharmaceutically acceptable carrier.

60. A diagnostic composition comprising an amount of the mutant TSH heterodimer of claim 13 sufficient to stimulate iodine uptake by thyroid cancer cells; and a pharmaceutically acceptable carrier.

61. A diagnostic composition comprising an amount of the mutant TSH heterodimer of claim 26 sufficient to stimulate iodine uptake by thyroid cancer cells; and a pharmaceutically acceptable carrier.

62. A diagnostic composition comprising an amount of the TSH analog of claim 30 sufficient to stimulate iodine uptake by thyroid cancer cells; and a pharmaceutically acceptable carrier.

63. A kit comprising in one or more containers a therapeutically effective amount of the mutant TSH heterodimer of claim 13, 26 or the TSH analog of claim 32.

64. A kit comprising in one or more containers a diagnostically effective amount of the mutant TSH heterodimer of claim 13 or 26 or the TSH analog of claim 32.

65. The nucleic acid of claim 40 or 42 which is isolated.

66. The composition of claim 57, 58, 60 or 61 in which the mutant TSH heterodimer is purified.

add A5

Add B1